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Prospective investigation of the neural risk factors for postoperative delirium using magnetic resonance imaging

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Prospective investigation of the neural risk factors for postoperative delirium using magnetic resonance imaging

Directed by Professor Jae-Jin Kim

The Doctoral Dissertation
submitted to the Department of Medical Science,
the Graduate School of Yonsei University
in partial fulfillment of the requirements
for the degree of Doctor of Philosophy

Jung Eun Shin

June 2015

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Jung Eun Shin

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

Prospective investigation of the neural risk factors for postoperative delirium using magnetic resonance imaging

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(Directed by Professor Jae-Jin Kim)

Delirium is an acute confusional state that is characterized by sudden alteration and fluctuation in consciousness and cognition associated with impaired attention. Delirium frequently occurs after surgery, particularly in patients undergoing hip fracture, however, the underlying neural mechanism remains uncertain. The present study aimed to investigate predictive neural correlates of postoperative delirium. Before surgery, patients with hip fracture were assessed for cognitive impairment and scanned using magnetic resonance imaging. After surgery, they were evaluated for postoperative delirium for 7 successive days and additional functional scans were performed on postoperative delirium onset or the end of assessment day according to postoperative delirium occurrence. Then anatomical and functional data were analyzed with voxel based morphometry, diffusion tensor imaging, and functional connectivity analysis. Patients with postoperative delirium had bigger total intracranial volume and ventricle volume, and smaller volume in the medial frontal gyrus, cingulate/precuneus, superior and transverse temporal gyrus, and caudate nucleus. These changes of brain areas were similar with Alzheimer's disease. In particular, the frontal areas, temporal areas, and caudate nucleus were more associated with MMSE scores. Patients with postoperative delirium also showed broadly reduced fractional anisotropy across the brain, including the superior and longitudinal fasciculus, corpus callosum, and external capsule. In functional connectivity, patients on delirious state showed greater association in the caudate nucleus and insula with the superior and transverse temporal regions, and there were negative correlations between Korean-Delirium Rating Scale and connectivity strength of the superior temporal gyrus and inferior frontal gyrus ($r = -0.672$, $p = 0.048$), and connectivity strength of the caudate nucleus and inferior frontal gyrus ($r = -0.633$, $p = 0.067$), respectively. This study suggests that cortical atrophy, particularly in the temporal areas and caudate nucleus, and overall impairment of cortical connections may be involved in postoperative delirium occurrence; nevertheless, increased connectivity of the bilateral temporal brain regions with the thalamo-cortical brain regions on delirious state could be interpreted as efforts to prevent persistent postoperative delirium and promote restoration of altered consciousness.

Key words: postoperative delirium, voxel based morphometry, diffusion tensor imaging, the temporal areas, the thalamo-cortical brain regions, functional connectivity

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I. INTRODUCTION

Delirium is an acute confusional state that is characterized by sudden alteration and fluctuation in consciousness and cognition associated with impaired attention. Patients with delirium usually experience severe disorganization of behavior, changes in arousal, and even psychotic symptoms such as hallucination. According to psychomotor type, delirium is classified into hyperactive, hypoactive, and mixed type. Hyperactive type is associated with increased activity level, wandering, irritability, and hallucination while hypoactive type is associated with decreased amount activity, reduced alertness, withdrawal, and decreased amount speech. In mixed type, patients show both hyperactive and hypoactive symptoms during a day. Delirium mostly disappears within a few days. However, its influence is enormous in terms of prognosis and economic costs.[1,2] Until recovery of delirium, duration of hospitalization becomes longer, early mobilization and rehabilitation are delayed, and even after recovery or discharge, cognitive decline may persist and mortality is increased within one year. Caregivers or family members also suffer emotional damage by patients. Delirium is gradually considered to be prevented. Above all, postoperative delirium has been focused on due to its sudden occurrence after surgery and aftereffects.

1. Postoperative delirium and its risk factors in patients with hip fracture

Until now, many research studies have been done to figure out risk factors for postoperative delirium. With including fluid and electrolyte abnormalities, infection, drug toxicity, metabolic disorders, and hypoxia,[3-5] operation-related conditions such as perioperative blood loss, severe pain, and poor postoperative mobility have been shown to be risk factors for postoperative delirium.[6-8] On the other hand, depending on surgical units, various indicent rates of postoperative delirium also have been reported. Among them, hip fracture surgery is the representative one due to its higher incident rates than other surgical units.[9] While patients in most surgical units experience postoperative delirium with 10 to 35%, patients undergoing hip fracture surgery usually experience postoperative delirium with 43 to 61% incident rate, which is similar ratio of patients who go through high risk heart surgery.[10,11] Among orthopedic unit, postoperative delirium occurs at a higher frequency to patients undergoing hip fracture surgery than to those undergoing elective hip surgery.[12] As hip fracture is one of the world-wide health problems, various countries report the incidence anywhere from 2 to 574 patients per 0.1 million people. Notably, hip fracture rate is increasing particularly in parts of Asia.[13,14] Considering the widespread of hip fracture, increased likelihood of developing postoperative delirium after hip fracture surgery, and the adverse impacts that postoperative delirium produces, prediction and prevention to postoperative delirium is essential for patients with hip fracture.

Like in other surgical units, older age and cognitive impairment are reported to be associated with postoperative delirium occurrence in studies of patients with hip fracture.[9] On the other hand, higher occurrence of postoperative delirium in patients who underwent hip fracture surgery than in patients who received other surgeries convey the possible existence of additional risk factors involved in the emergence of the disease. Because patients with hip fracture are more prone to osteoporosis, they usually experience traumatic events such as fracture from falling down on iced road.[12,15] They are also exposed to the sounds of a drill or hammer during surgery and such unexpected situations may provoke psychological disturbances in patients, leading to postoperative delirium. Although the contribution of psychological factors to postoperative delirium have been rarely considered in the delirium study,[16] there are a few results that preoperative anxiety and major depression were predictive factors for postoperative delirium.[17,18] In terms of the relationship with personality, only one report showed that Type D personality, which is characterized by social inhibition and negative affect, had a nearly significant association with postoperative delirium.[17] In our previous study, neuroticism, which is more likely to experience anxiety, anger, guilt, and depressed mood, remained a predictive factor for postoperative delirium in patients with hip fracture. Taken together, there are number of risk factors for postoperative delirium and especially in patients with hip fracture, and not only medical and physical aspects, but also psychological one should be considered.

2. Neuropsychological findings of postoperative delirium in magnetic resonance imaging studies

Although the etiology of postoperative delirium is still yet to be revealed and risk factors for postoperative delirium are under debate, there is no doubt that its influence has far-reaching implications. By comparison, neuropsychological studies on postoperative delirium are very few and mainly focus on association with aftereffects of postoperative delirium. A study showed that longer duration of delirium during hospitalization was associated with state of long-term cognitive impairment and greater atrophy in brain regions, including the hippocampus and superior frontal lobes, which had been scanned 3 months after hospital discharge.[19] In diffusion tensor imaging, increased duration of postoperative delirium was associated with some white matter disruptions, including the genu and splenium of the corpus callosum and anterior limb of the internal capsule.[20] However, in functional magnetic resonance imaging, there was no association between delirium-related scales and brain region activities during working memory task either at discharge or after 3 months.[21] These studies above had two limitations. First, their time period of interest was on post-resolution delirious state at discharge or beyond discharge, therefore the contribution of preoperative state to episode delirium cannot be concluded. Second, in the case of functional data, task-based functional imaging did not adequately provide cerebral connectivity changes at resting state. A study made further improvements by adjusting time period of interest earlier to the period between before and after the surgery and reported that subcortical white matter hyperintensity and new postoperative ischemic lesions were significantly associated with postoperative delirium in patients who had undergone cardiac surgery.[22] There was also a functional imaging study during an episode of postoperative delirium.[23] It suggested that the disruption in reciprocity of the dorsolateral prefrontal cortex with the posterior cingulate and reduced functional connectivity of the thalamus and caudate nucleus with other subcortical regions during postoperative delirium may underlie the pathophysiology of postoperative delirium. These two imaging studies are a striking achievement on delirium research and provide important knowledge from anatomical and functional aspects. However, questions of whether there are pre-existing differences in anatomical and functional state between delirious and non-delirious group, and whether there are some contributions to postoperative delirium occurrence still remain unresolved. To answer these problems, all types of magnetic resonance imaging are considered using prospective approach.

3. Possibility of the existence of neural correlates that predict postoperative delirium

Although study to find out predictive neural correlates for postoperative delirium occurrence has never been done, the possibility of their existence could be derived from some results of clinical researches.[5,24,25] As mentioned earlier, older age and cognitive impairment are reported to be strongly associated with delirium.[26] These two factors have been commonly concerned in neurologic and psychiatric disorder, particularly, for Alzheimer's disease. Although delirium is different from Alzheimer's disease in terms of some characteristics, such as sudden onset, short time of period and possibility of retrieval, they share some features, such as loss of orientation and impairment in memory, emotion and behavioral control. Considering that many patients with delirium also report to have Alzheimer's disease, neural correlates predicting delirium may exist in brain regions associated with Alzheimer's disease.

Anatomical and functional magnetic resonance imaging studies have shown that patients who have progressive cortical atrophy,[27-29] reduced white matter integrity,[30] metabolism change,[31] and altered functional connectivity[32,33] in the brain would likely to develop to Alzheimer's disease. In voxel based morphometry, patients with Alzheimer's disease yielded reduced volume in some brain regions, including the hippocampus, parahippocampus, temporal and cingulate gyrus, precuneus, insula, caudate nucleus and frontal cortex.[34,35] Fractional anisotropy was lower in the genu and splenium of corpus callosum, as well as frontal, temporal, and parietal lobes.[36,37] In resting state functional magnetic resonance imaging, compared to amnestic mild cognitive impairment patients and comparison group, patients with Alzheimer′s disease showed decreased connectivity strengths in the default mode network and fronto-parietal network, while exhibiting increased connectivity in the executive network and salience network.[32] Although anatomical and functional changes in Alzheimer′s disease were mainly performed by each modality, these previous results about Alzheimer′s disease are important to compare with results of delirium and their interpretation.

4. Magnetic resonance imaging and analysis

To examine anatomical neural correlates for a disease, voxel based morphometry has been used because of its ability to measure gray matter volume to investigation of focal differences in brain anatomy on voxel level.[38] Voxel based morphometry facilitates group analysis through spatial normalization and smoothing to reduce individual differences in the brain. Diffusion tensor imaging enables measurements of the restricted diffusion of water in tissue to produce neural tract images.[39] Fractional anisotropy is the value that describes the degree of anisotropy of a diffusion process. A value of one means that diffusion occurs only along one axis and it is fully restricted along all other directions. Therefore, fractional anisotropy is thought to reflect fiber density in white matter because the neural axons of white matter have an internal fibrous structure analogous to the anisotropy. Water molecules in the direction aligned with the internal fibrous structure will diffuse more rapidly than in relatively reduced density of internal structure or in perpendicular to the preferred direction, showing higher fractional anisotropy.

Meanwhile, functional magnetic resonance imaging would be a key technique to anticipate postoperative delirium because it could measure altered spontaneous neuronal activity by detecting associated changes in blood flow. Its concept builds on the principle, which explains that increased neuronal activity leads to increase in local blood flow, oxygen-rich blood to those brain regions, and improvement of magnetic resonance signal. Among methods of functional brain imaging, resting state functional magnetic resonance imaging can be used to investigate brain functional connectivity when an individual is on restful state since brain activity continues to persist even in the absence of an explicit task, thus any brain regions with spontaneous neuronal activity would be seen.[40-42] In this sense, the resting state approach is useful when exploring such brain regions and their organization. There have been numerous resting state functional connectivity researches that revealed a number of networks, such as default mode network, salience network and executive network in healthy subject, as well as in patients with neurological or psychiatric diseases with altered patterns.[32,43] Considering that postoperative delirium is temporary and has relatively short symptom duration, it suggests that functional imaging captures distinctive patterns during delirious state compared with non-existence, and even shows functional differences with Alzheimer's disease. Altogether, these three types of imaging techniques are essential to the comprehension of postoperative delirium.

5. Objective: The investigation of neural correlates of postoperative delirium in patients with hip fracture

In order to examine predictive neural correlates of postoperative delirium in patients with hip fracture, we recruited participants, interviewed them and their family members, and scanned enrolled patients using magnetic resonance imaging prior hip surgery to obtain each patient's ordinary functional state of the brain with anatomical information. Patients were assessed for delirium for a week after the surgery, divided into two groups according to delirium occurrence, and were scanned again for additional functional imaging. Then we performed a detailed investigation of gray matter voxel-based morphometry and white matter tract-based spatial statistics. To identify the involvement of Alzheimer′s disease in postoperative delirium occurrence, scores for cognitive impairment were used as covariate or not on voxel based morphometry. Functional connectivity in the brain at rest state was conducted with the brain regions having significant group differences on cortical volume as seeds. Overall functional connectivity patterns with significance were integrated with seeds. Finally, the correlation analysis between delirium related clinical scales and neural data was performed.

II. MATERIALS AND METHODS

1. Subjects and preoperative characteristic data

The Institutional Review Board of Yonsei University Gangnam Severance Hospital approved the study protocol and the study was conducted from September 2013 until July 2014. Among 809 orthopedic patients, 200 patients diagnosed with femur fracture were eligible for the study. Twenty-nine patients were not screened due to missing and transfer to another hospital. Of the 171 patients with hip fracture who were screened, 80 were excluded based on the exclusion criteria such as age < 70 years, communication difficulties, severe brain damage, acute brain hemorrhage or neurology disease, and 18 were declined. After 73 provided written informed consent, 15 were not enrolled for some reasons such as incomplete interview, delirium before surgery and withdraw. The final study sample consisted of the remaining 58 patients (Figure 1). Brief characteristic information including age, gender, duration of education, medical history, family history, and hospitalization duration was collected by patients, their family member, or medical record. To measure cognitive impairment, Mini-Mental State Examination (MMSE) was used which was 30-point. Lower scores, more severe is cognitive impairment.[44] We categorized patients who had MMSE scores < 20 into probable dementia group even though they had never been diagnosed with dementia.

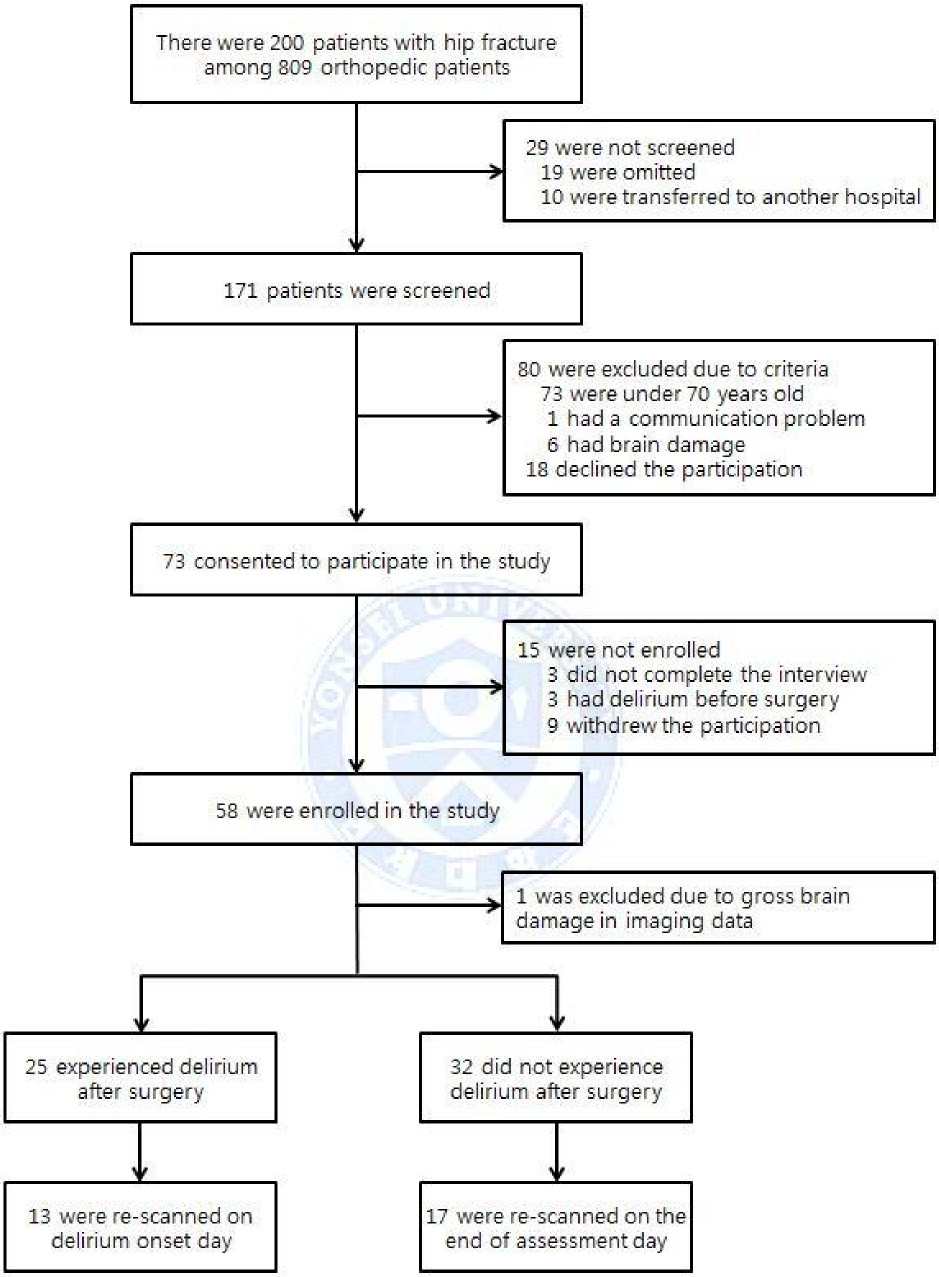

Figure 1. Study enrollment flow. Among 809 orthopedic patients, 58 were enrolled in the analysis.

2. Assessment of postoperative delirium

For delirium diagnosis and its severity assessment, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and Korean-Delirium Rating Scale-R-98 (K-DRS) were used by a trained psychiatrist.[45,46] K-DRS consists cognitive and non-cognitive items, and higher scores mean more severe delirium. Every patient was evaluated for delirium from the next morning after hip surgery for 7 successive days at intervals of 24hrs. The 7-day study period was determined by other studies. For continuous delirium assessment, the confusion assessment method (CAM) was used.[47] The CAM is a well-validated instrument for the diagnosis of delirium. It includes 4 items following: (1) an acute onset and fluctuation course of mental state; (2) inattention; (3) disorganized thinking; (4) altered level of consciousness. For a positive diagnosis, 1 and 2 item were satisfied essentially and 3 or 4 item selectively. When patients were diagnosed with postoperative delirium, they were re-scanned on the onset day while patients who did not experience postoperative delirium were re-scanned on the 7th day after surgery. Additional scans were done using only functional magnetic resonance imaging.

3. Imaging data acquisition

All images were collected using a Sigma EXCITE 3-T MR system (GE, Milwaukee). A high-resolution T1-weighted anatomical image was obtained using a spoiled gradient-echo sequence (matrix = 256 x 256, echo time = 3.2

ms, repetition time = 8.2 ms, field of view = 240 mm, slice thickness = 1.2 mm, flip angle = 12°, number of slices = 136) to serve as an anatomical underlay for the brain activity and to be used for gray matter volume analysis. Diffusion tensor images were acquired using single-shot echo-planar acquisition (matrix = 128 x 128, echo time = minimum, repetition time = 8000 ms, field of view = 240 mm, slice thickness = 2.6 mm). Diffusion was measured along 16 directions.

Functional images were obtained using over 5 minutes using gradient-echo echo-planar imaging sequences (matrix = 64 x 64, echo time = 17.6 ms, repetition time = 2,500 ms, field of view = 240 mm, slice thickness = 3 mm, flip angle = 90°, number of slices = 50). All patients were instructed to rest with their eyes closed during the scan. Fifty eight participants underwent fMRI scanning (25 in the patient group, 33 in the comparison group), but data from one comparison subject was excluded in all imaging analysis because of history of gross brain hemorrhage damage (25 in the patient group, 32 in the comparison group). Then, data from two patient subjects were additionally excluded in DTI analysis because of technical problems (23 in the patient group, 32 in the comparison group). In fMRI analysis, data from one patient subject was excluded because of imaging problems (24 in the patient group, 32 in the comparison group).

4. Voxel-based morphometry (VBM) analysis

VBM analysis was performed to compare gray matter volumes between patients with and without postoperative delirium using SPM12 software (Institute of Neurology, University College London, London, England). Subject images were visually inspected for any artifacts or anatomical abnormalities. T1-weighted MR images were segmented into gray matter, white matter and cerebrospinal fluid using the SPM12 default segmentation model. Then, the segmented gray matter images were nonlinearly normalized to the gray matter templates and these normalization parameters were reapplied to the T1-weighted MR images of each subject to perform spatially transformed to Montreal Neurological Institute (MNI) space. Next, the normalized, segmented gray matter images were Jacobian scaled to correct for volume changes in nonlinear normalization and then smoothed with a 6 mm full-width at half-maximum isotropic Gaussian kernel. Finally, regional volume differences at each voxel in the gray matter between two groups were determined with age, sex, MMSE scores, and total intracranial volume as covariates. Additionally, to identify the effect of cognitive impairment on postoperative delirium occurrence, same analysis was done with MMSE scores excluded. The volume of total intracranial volume was calculated using a program developed in-house which run on Matlab. The threshold for the resulting statistical map was set at uncorrected $p < 0.001$ with an 130 contiguous voxels which was met the $p < 0.05$ criteria corrected by cluster level for multiple comparisons as estimated by 10,000 Monte Carlo simulations using AlphaSim program.[48] Partial correlation analysis between gray matter volume density and delirium related characteristics was performed in patients with postoperative delirium with age, gender, MMSE scores, and total intracranial volume as covariates.

5. Diffusion tensor imaging (DTI) data analysis

For voxel-based analyses of white matter structure across the whole brain, the tract-based spatial statistics analysis was performed with the FMRIB Software Library (FSL) software package version 4.1.[49] Raw DTI data was corrected for eddy current correction and brain-extracted. Then fractional anisotropy images were created by fitting a tensor model to the raw diffusion data using FMRIB′s Diffusion Toolbox (part of FSL). Then, all participants' fractional anisotropy data was aligned in the MNI space using the nonlinear registration. And the mean fractional anisotropy image was created and thinned to produce a mean fractional anisotropy skeleton with a threshold of fractional anisotropy > 0.2. Each participant′s aligned fractional anisotropy images were then projected onto this skeleton. Voxel-wise statistical analyses were performed using 10,000 randomized permutations with Threshold-Free Cluster Enhancement (TFCE) approach. The 95th percentile was used as cluster-size threshold and fully corrected for multiple comparisons ($p < 0.05$; TFCE-corrected). We used the Johns Hopkins University DTI-based white matter atlases and the ICBM-DTI-81 white matter labels atlas for anatomic labeling. In addition, to investigate white matter integrity that is associated with delirium related characteristics, voxelwise correlation analysis was performed between fractional anisotropy values and delirium related variables. Age, gender, MMSE scores, and total intracranial volume were used as covariates for all statistics.

6. functional magnetic resonance imaging (fMRI) data analysis

Image processing was performed using the Analysis of Functional NeuroImages software package (http://afni.nimh.nih.gov/afni). The time series data for the first ten seconds were discarded to eliminate any signal decay associated with the magnetization reaching equilibrium. After slice timing and realignment for motion correction, the corrected images were coregistered to the T1-weighted image for each subject. The T1-weighted images were then normalized to the standard T1 template. Then, the coregistered images were normalized from spatial normalization of the T1-weighted images. To remove nonspecific effects such as physiological behaviors and nuisance variables were regressed out. The motion component was also regressed out. Then preprocessed and regressed out functional images were temporally band-pass filtered with 0.009-0.08 Hz to reduce low frequency fluctuations in the blood-oxygen-level-dependent signal. Finally, the images were smoothed using a Gaussian filter with a 6-mm full-width at half-maximum.

For seed-based analysis, five brain regions which survived at corrected at $p < 0.05$ in VBM analysis were used as seeds. Voxel-wise correlations were conducted between the times series for each seed and the whole brain. The value of functional connectivity was generated by converting the correlation coefficients to z values. To confirm seeds related connectivity during resting state before and after surgery, one-sample t-test was performed for each group with a significance threshold of $p < 0.001$ uncorrected across the whole brain. Then to find out neural correlates showing group difference, independent-sample t test was done with a significance threshold of uncorrected $p < 0.001$ with more than 35 voxels. The partial correlation analysis was conducted to examine the association between functional connectivity strengths and delirium related characteristics. All statistical analysis was performed with age, gender, gray matter volume and MMSE score as covariates.

III. RESULTS

1. Characteristics of patients according to postoperative delirium occurrence

As shown in Table 1, there were no statistical differences in age, gender, education duration, cognitive diagnosis, past history, and family history between two groups. In terms of cognitive impairment, while either the proportion of participants who were diagnosed with dementia or the proportion of participants developing dementia was not significant between groups, MMSE scores in patients with postoperative delirium were significantly lower than those without postoperative delirium ($t = 2.41$, $p < 0.05$).

Patients who experienced postoperative delirium mostly showed its symptoms on postoperative day 2 (range: postoperative day 1-5), and lasted 4 days (range: postoperative day 1-33). The K-DRS scores ranged from 12 to 28. In motor subtype of delirium, most patients were included in mixed type (n=12, 48%), and then followed by hypoactive (n=9, 36%) and hyperactive type (n=4, 16%) , respectively.

Table 1. Characteristics of participants according to postoperative delirium

Characteristic	All patients (n=57)	Delirious (n=25)	Non-delirious (n=32)	*p*
Demographics				
Age, years[1]	82.1±6.5	83.7±6.1	80.9±6.6	0.11‡
Proportion of Female sex	82.5%	72.0%	90.6%	0.09†
Education, years[2]	6 (0-16)	9 (0-16)	6 (0-16)	0.39∮
Cognitive diagnosis				
Definite dementia	24.6%	32.0%	18.8%	0.25†
Probable dementia	49.1%	60.0%	40.6%	0.15†
Past history				
Major mental disorder	14.0%	20.0%	9.4%	0.28†
Delirium	10.9%	16.0%	6.7%	0.39†
Other mental disorder	3.5%	4.0%	3.1%	1.00†
Brain injury	16.1%	12.0%	19.4%	0.72†
Family history				
Major psychiatric disease	24.6%	32.0%	18.8%	0.25†
Cognitive measure				
MMSE, scores[1]	18.7±6.5	16.5±6.3	20.5±6.2	0.02‡

MMSE, Mini-Mental State Examination
[1] mean (standard deviation)
[2] median (range)
‡ p value of Student t-test
∮ p value of Mann-Whitney U test
† p value of Pearson's chi-square test

2. Group comparison of brain volume according to postoperative delirium occurrence

Brain volume was compared between patients with and without postoperative delirium (Table 2). Patients with postoperative delirium had significantly more amount total intracranial volume than that of patients without one (t = 2.78, p = 0.01). In detail, ventricle volume was bigger in delirious patients than non-delirious ones (t = 4.81, p < 0.001). However, there were no differences of gray matter volume and white matter volume between two groups.

Table 2. Brain volume in patients with and without postoperative delirium (unit= ml)

Volume characteristics	Delirious (n=25)	Non-delirious (n=32)
Total intracranial volume	1590.2 ± 124.3[1]	1505.7 ± 105.7[*]
White matter volume	318.4 ± 58.9	316.5 ± 53.1
Gray matter volume	641.5 ± 60.8	653.9 ± 71.4
Cerebral spinal fluid volume	630.4 ± 74.3	535.3 ± 73.9[**]

[1] mean±standard deviation
* p < 0.05 with student t-test between two groups , ** p < 0.001 with student t-test

3. Group differences in gray matter volume using VBM

According to inclusion of MMSE scores as a covariate, gray matter regions showing differences between groups are shown in Table 3 and 4.

With MMSE scores, patients with postoperative delirium showed significantly decreased gray matter concentrations in the medial frontal gyrus, cingulate gyrus, precuneus, superior and transverse temporal gyrus, and caudate nucleus. In contrast, there was no gray matter region with higher concentration in patients with postoperative delirium than patients without one. In correlation analysis, correlations between gray matter volume, and delirium onset, duration, severity or hospitalization duration did not show any significance. On the other hand, without MMSE scores, patients with postoperative delirium showed relatively more brain regions with decreased gray matter concentrations, including the superior frontal gyrus, postcentral gyrus, middle temporal gyrus, hypothalamus and cerebellum. Even in same brain regions, decreased concentration in the temporal areas and caudate nucleus more was expanded than when MMSE scores as a covariate. There was also no gray matter region with higher concentration in patients with postoperative delirium than patients without one.

Table 3. Brain regions with decreased volume in postoperatively delirious patients compared with non-delirious patients controlling for cognitive deficits

Brain region (Brodmann area)	Nvox	Zmax	MNI coordinates		
			x	y	z
Medial frontal gyrus (6)	223	3.95	-2	-24	66
		3.86	-3	-18	56
Cingulate gyrus/precuneus (31/7)	148	3.56	11	-36	39
		3.31	6	-35	48
Superior temporal gyrus (22)	297	3.86	56	5	-36
Transverse temporal gyrus (41)	165	3.79	-35	-27	12
Caudate nucleus	748	4.24	-12	8	14
		4.17	-18	-9	24

Nvox, the number of voxel; Zmax, X maximum within a cluster; MNI, Montreal Neurological Institute

Corrected $p < 0.05$ by a cluster level threshold is equivalent to uncorrected $p < 0.001$ and more than 130 voxels.

Age, gender, MMSE scores, and total intracranial volume were used as covariates.

Table 4. Brain regions with decreased volume in postoperatively delirious patients compared with non-delirious patients without controlling for cognitive deficits

Brain region (Brodmann area)	Nvox	Zmax	MNI coordinates		
			x	y	z
Medial frontal gyrus (6)	229	4.13	-2	-23	68
	155	4.26	-17	11	59
Superior frontal gyrus (8)	131	3.89	-5	35	47
	138	4.09	8	21	53
Postcentral gyrus (3)	152	4.00	26	-29	56
Cingulate gyrus/precuneus (31/7)	349	4.30	5	-30	39
		4.05	6	-36	48
Superior temporal gyrus (38)	712	4.24	-39	9	-38
Middle temporal gyrus (21)	974	4.67	45	5	-39
	959	4.63	-56	-24	-15
Transverse temporal gyrus (41)	289	4.47	-36	-27	11
Caudate nucleus	1673	5.24	-21	-8	23
Hypothalamus	186	3.89	-3	2	-14
Cerebellum	185	3.79	-42	-72	-54

Nvox, the number of voxel; Zmax, X maximum within a cluster; MNI, Montreal Neurological Institute

Corrected $p < 0.05$ by a cluster level threshold is equivalent to uncorrected $p < 0.001$ and more than 130 voxels.

Age, gender, and total intracranial volume were used as covariates.

4. Group differences in FA value using DTI

Compared with patients without postoperative delirium, those with postoperative delirium showed broadly reduced fractional anisotropy across the brain. Fractional anisotropy in bilateral body of corpus callosum, left inferior longitudinal fasciculus, bilateral superior longitudinal fasciculus and external capsule was significantly decreased in delirious group (Figure 2). However there was no increased fractional anisotropy in patients with postoperative delirium in comparison to that of the patients without one. There was also no correlation between fractional anisotropy and delirium onset, duration, severity or hospitalization duration.

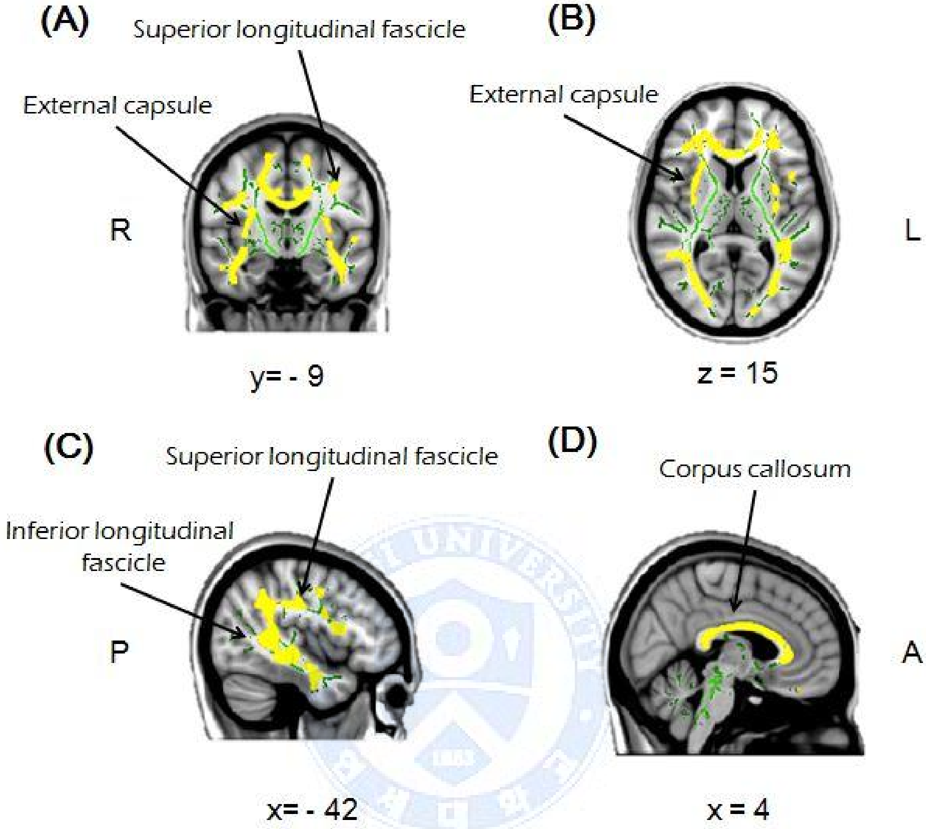

Figure 2. Group comparison of fractional anisotropy values between patients with and without postoperative delirium. Decreased fractional anisotropy values in (A) the superior longitudinal fascicle, (B) external capsule, (C) inferior longitudinal fascicle, and (D) corpus callosum in patients with postoperative delirium were shown in yellow (p < 0.05, TFCE with age, gender, total intracranial volume and MMSE scores as covariates). Mean fractional anisotropy skeleton was represented in green.
R, right; L, left; P, posterior; A, anterior

5. Group differences of functional connectivity before surgery using fMRI

The group comparisons of functional connectivity before surgery are shown in Table 5. When using the medial prefrontal gyrus as a seed, patients with postoperative delirium showed a greater association only in the precuneus. With the superior temporal gyrus as a seed, patients with postoperative delirium showed a lower correlation in the superior frontal gyrus. When the transverse temporal gyrus was used as a seed, there was a lower correlation in the middle occipital gyrus and a greater correlation in the precentral gyrus. However, when using the cingulate gyrus/precuneus and caudate nucleus as seeds, there was no brain region showing significant correlation before surgery in between-group comparison.

Table 5. Brain regions showing functional connectivity strength with each seed between patients with and without postoperative delirium before surgery

Seed	Comparison	Brain region	Nvox	Zmax	MNI coordinates		
					x	y	z
Medial frontal gyrus	Delirious > Non-delirious	Precuneus (19)	56	3.89	18	-83	45
Superior temporal gyrus	Non-delirious > Delirious	Superior frontal gyrus (8)	54	3.86	28	28	50
Transverse temporal gyrus	Non-delirious > Delirious	Middle occipital gyrus (19)	60	4.15	-28	-89	17
	Delirious > Non-delirious	Precentral gyrus (6)	54	-3.71	-24	-15	75

BA, Brodmann area; Nvox, the number of voxel; Zmax, X maximum within a cluster; MNI, Montreal Neurological Institute

Brain region with uncorrected $p < 0.001$ and more than 35 voxels are reported with age, gender, gray matter volume and MMSE scores as covariates.

6. Group differences of functional connectivity after surgery using fMRI

A. Seed-based functional connectivity in each group

After surgery among 25 patients with postoperative delirium, 13 patients were re-scanned and among 32 patients who did not experience postoperative delirium, 17 patients were re-scanned. When comparing characteristics between this two groups after surgery, the difference in MMSE scores only remained significant ($t = 2.05$, $p = 0.05$), and there was no significant difference in other characteristics such as general demography, cognitive diagnosis, past history, and family history (Table 6). By using five brain regions as seeds, which were from VBM results when MMSE scores were included as a covariate, the one-sample t-test results of functional connectivity with each seed are shown in Figure 3. Overall, patients without postoperative delirium showed more and broader brain regions having positive or negative correlations with each seed in comparison to patients with one. In addition, relative to before surgery, there were likely to have less and smaller brain regions having significant correlations with each seed after surgery.

Table 6. Characteristics of participants who were re-scanned for fMRI

Characteristic	Delirious (n=25)	Non-delirious (n=32)	*p*
Demographics			
Age, years[1]	84.5±6.7	81.7±7.2	0.30‡
Proportion of Female sex	61.5%	88.2%	0.19†
Education, years[2]	9 (0-16)	6 (0-16)	0.31∮
Cognitive diagnosis			
Definite dementia	30.8%	23.5%	0.70†
Probable dementia	61.5%	35.3%	0.15†
Past history			
Major mental disorder	30.8%	17.6%	0.67†
Delirium	7.7%	5.9%	1.00†
Other mental disorder	7.7%	5.9%	1.00†
Brain injury	15.4%	23.5%	0.67†
Family history			
Major psychiatric disease	38.5%	23.5%	0.44†
Cognitive measure			
MMSE, scores[1]	16.1±6.9	21.2±6.6	0.05‡

MMSE, Mine-Mental State Examination
[1] mean (standard deviation)
[2] median (range)
‡ p value of Student t test
∮ p value of Mann-Whitney U test
† p value of Pearson's chi-square test

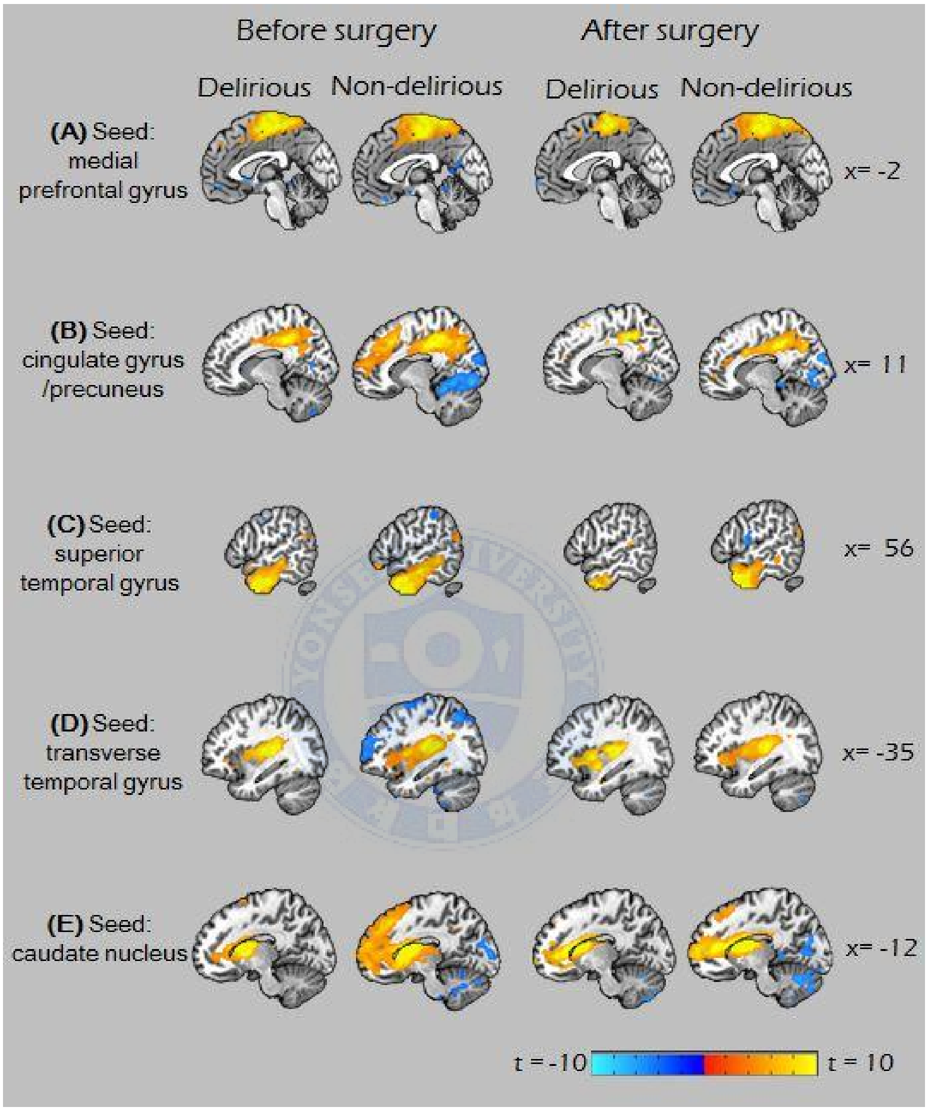

Figure 3. Brain regions showing seed-based voxel-wise significance of correlations in each group before and after surgery. (A) the medial frontal gyrus, (B) cingulate gyrus/precuneus, (C) superior temporal gyrus, (D) transverse temporal gyrus, and (E) caudate nucleus were used as seeds. One-sample t-test was performed with the threshold of significant at uncorrected $p < 0.001$.

B. Group differences of functional connectivity

Brain regions showing significant functional connectivity with each seed between group comparisons after surgery are shown in Table 7. When the superior temporal gyrus was used as a seed, relative to comparison subjects, there were lower correlations in the precuneus, supramarginal gyrus, and cerebellum and greater correlations in the inferior frontal gyrus and supramarginal gyrus. When the transverse temporal gyrus was used as a seed, relative to non-delirious patients, more decreased correlations were shown in the fusiform gyrus and cerebellum and more increased correlations were shown in the middle frontal gyrus, insula, and caudate nucleus in delirious patients. When the caudate nucleus was taken as a seed, patients with postoperative delirium showed greater associations with the inferior frontal gyrus and insula than patients without one after surgery. On the other hand, when using the medial frontal gyrus and cingulate gyrus/precuneus as seeds, there was no brain region showing significant correlation in between-group comparison. Table 8 shows brain regions having significant difference in functional connectivity with each seed in patients with postoperative delirium before and during delirious state. When the superior temporal gyrus was used as a seed, relative to before surgery, there was a significantly lower correlation in the posterior cingulate and a greater correlation in the middle frontal gyrus after surgery. When the caudate nucleus was used as a seed, greater correlations were observed in the anterior cingulate gyrus, caudate nucleus, inferior frontal gyrus, and superior temporal gyrus during postoperative delirious state than on pre-operative state. However, there was no brain region showing significant correlation when the medial frontal gyrus, cingulate gyrus/precuneus, and transverse temporal gyrus were used as seeds.

To comprehend overall functional connectivity with seeds, as shown in Figure 4, all patterns of significant functional connectivity were presented with brain regions which survived at AlphaSim corrected $p < 0.05$ in VBM.

Table 7. Brain regions showing functional connectivity strength with each seed between patients with and without postoperative delirium after surgery

Seed	Comparison	Brain region (BA)	Nvox	Zmax	MNI coordinates		
					x	y	z
Superior temporal gyrus	Non-delirious > Delirious	Precuneus (31)	179	5.11	-8	-59	27
		Supramarginal gyrus (39)	48	4.34	50	-53	23
		Cerebellum	138	5.06	4	-63	-32
	Delirious > Non-delirious	Inferior frontal gyrus (10)	42	4.44	36	38	13
		Inferior frontal gyrus (47)	83	4.46	30	22	-2
		Supramarginal gyrus (40)	45	4.42	60	-45	33
Transverse temporal gyrus	Non-delirious > Delirious	Cerebellum	172	5.18	36	-63	-56
		Fusiform gyrus (18)	41	4.25	-20	-95	-20
	Delirious > Non-delirious	Insula	225	4.71	-34	8	9
		Caudate nucleus			-8	12	10
		Middle frontal gyrus (9)	55	4.10	-44	2	31
Caudate nucleus	Delirious > Non-delirious	Inferior frontal gyrus (11)	43	4.40	4	36	-16
		Insula (13)	95	4.01	34	-25	15

BA, Brodmann area; Nvox, the number of voxel; Zmax, X maximum within a cluster; MNI, Montreal Neurological Institute
Brain region with uncorrected $p < 0.001$ and more than 35 voxels are reported with age, gender, gray matter volume and MMSE score as covariates.

Table 8. Brain regions showing functional connectivity strength with each seed in patients with postoperative delirium before and after surgery

Seed	Comparison	Brain region (BA)	Nvox	Zmax	MNI coordinates		
					x	y	z
Superior temporal gyrus	Pre op. > post op.	Posterior cingulate gyrus (30)	43	6.69	-10	-57	7
	Post op. > pre op.	Middle frontal gyrus (9)	57	9.17	-36	42	37
				8.11	-46	34	35
Caudate nucleus	Post op. > pre op.	Anterior cingulate gyrus (24)	807	17.97	4	24	-2
		Caudate nucleus			11	15	18
		Inferior frontal gyrus (47)	63	7.24	-16	32	-12
		Superior temporal gyrus (38)	112	9.15	-52	16	-14

BA, Brodmann area; Nvox, the number of voxel; Zmax, X maximum within a cluster; MNI, Montreal Neurological Institute

Brain region with uncorrected $p < 0.001$ and more than 35 voxels are reported with age, gender, gray matter volume and MMSE scores as covariates.

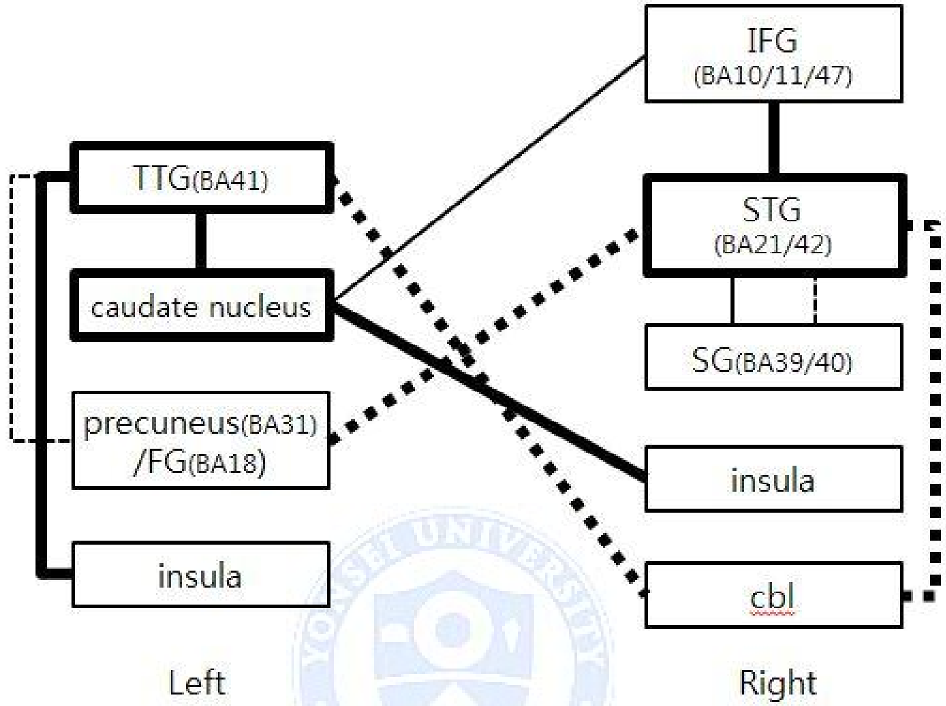

Figure 4. Summary of functional connectivity between brain regions during postoperative delirium. Box with bold border means a seed area; solid line means increased functional connectivity while dotted line means decreased functional connectivity; bold line means functional connectivity which survived at AlphaSim corrected $p < 0.05$.

TTG, transverse temporal gyrus; IFG, inferior frontal gyrus; STG, superior temporal gyrus; SG, supramarginal gyrus; FG, fusiform gyrus; cbl, cerebellum; BA, Brodmann area

C. Partial correlations between functional connectivity and clinical variables

As shown in Figure 5, patients with postoperative delirium showed significant correlations between the functional connectivity strength of each seed and the severity of delirium, and the duration of delirium. When the superior temporal gyrus was used as a seed, a negative correlation was shown between functional connectivity strength with the inferior frontal gyrus and K-DRS ($r = -0.672$, $df = 8$, $p = 0.048$), while a marginally significant positive correlation was presented in the cerebellum ($r = 0.646$, $df = 8$, $p = 0.060$). In terms of delirium duration, a negative correlation was shown in the supramarginal gyrus ($r = -0.735$, $df = 8$, $p = 0.024$). Additionally, when the caudate nucleus was selected a seed, there was also a negative correlation between functional connectivity strength with the inferior frontal gyrus and K-DRS with marginal significance ($r = -0.633$, $df = 8$, $p = 0.067$).

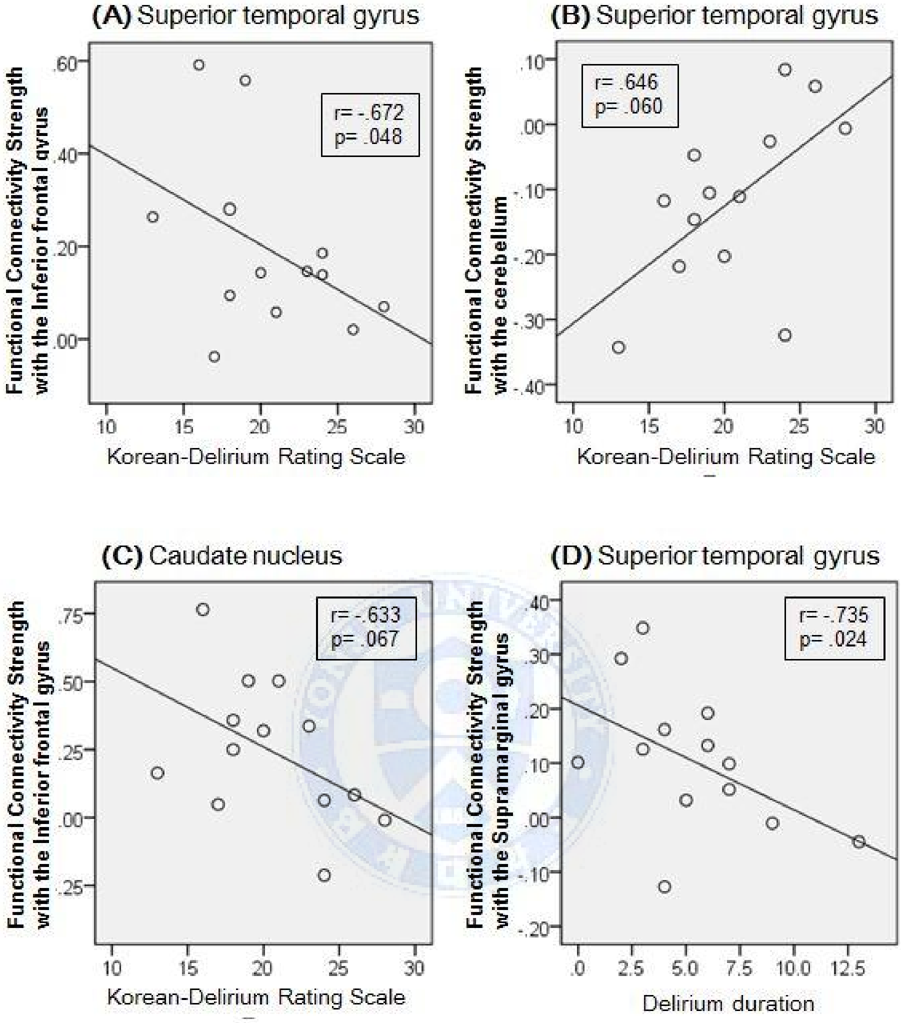

Figure 5. Association of the severity and duration of postoperative delirium with functional connectivity strength in brain regions. The inferior temporal gyrus (A, B, and D) and caudate nucleus (C) were used as seeds, respectively.

IV. DISCUSSION

To explore neural correlates that predict postoperative delirium in elder patients with hip fracture, we collected brief characteristics and clinical data, scanned participants' brains using anatomical and functional magnetic resonance imaging, and analyzed concentrations of gray and white matter and functional connectivity among the brain regions.

Among clinical characteristics, only MMSE scores that were measured before surgery was significant lower in postoperatively delirium group than non-delirium group. Although each group had similar distribution ratio of definite dementia or probable dementia, present study showed a stronger association between the severity of cognitive impairment and postoperative delirium occurrence. Of enormous clinical studies to find out risk factors for postoperative delirium, cognitive impairment was one of most frequently reported risk factors.[24,25] In addition, our results showed that patients with postoperative delirium had relatively larger total intracranial volume and ventricle volume than the volumes of patients without postoperative delirium. Higher total intracranial volume may be attributed to ventricle volume because remaining volume of gray matter and white matter were not significantly different from two groups. This result corresponded to an Alzheimer disease study, where patients with Alzheimer disease had increased ventricle volume and total intracranial volume.[27] So our study may shed some light on the reason why cognitive impairment is an important risk factor for postoperative delirium because patients with postoperative delirium actually have anatomical changes, which is similar to Alzheimer disease.

In VBM, there were two results according to MMSE scores as a covariate. Regardless of MMSE scores, the volumes of the precuneus, temporal gyrus, frontal gyrus, and caudate nucleus were more decreased in delirium group than non-delirium group, which resembles the results of Alzheimer's disease.[34,35] When MMSE scores were not included in covariates, only temporal lobe sub-regions were listed in both newly appearing brain regions with decreased concentration and existing brain regions with decreased concentration, which are more expanded than when MMSE scores were included. Altogether, temporal areas were the most brain regions associated with cognitive impairment as well as postoperative delirium occurrence. In functional connectivity, there were also the most significant changes between group comparisons when temporal lobe sub-regions were used as seeds. After surgery, there were greater positive correlations with the caudate nucleus, inferior frontal gyrus and insula in delirious patients than non-delirious patients. Such connectivity changes were also shown partially in the inferior frontal gyrus when the caudate nucleus was selected a seed. In diffusion tensor imaging, overall decreased fractional anisotropy was observed in postoperatively delirious patients, especially in the superior and inferior longitudinal fasciculus, which they connect between frontal and temporal regions, as well as the corpus callosum, and external capsule. Altogether, it is implied anatomical or functional associations between the temporal gyrus, caudate nucleus, insular, and inferior frontal gyrus.

First, the caudate nucleus is one of the main input regions for the basal ganglia and belongs to prefrontal loop among thalamo-cortical loops since it mainly receives axons from frontal cortex, including the lateral orbitofrontal cortex and dorsolateral prefrontal cortex, as well as from nearly all parts of cortex to thalamus.[50-52] Functionally, the caudate nucleus has association with these two prefrontal cortices[53] and our result was also confirmed on each group with the caudate nucleus as a seed. Functional connectivity studies have suggested that the involvement of the thalamo-cortical connectivity in disorders of consciousness or anesthetic-induced unconsciousness.[54-57] Even in a vegetative study, restoration of thalamo-cortical connectivity was associated with recovery from vegetative state, where negative connectivity correlation was switched to positive one and its connectivity change on recovery state is similar with that of comparison group.[58] In our results of within-group comparison, patients on delirious state showed significantly greater association within the caudate nucleus compared with those before delirium. However, it did not remain significant in after surgery between-group comparison. It may be interpreted that the caudate nucleus in patients with postoperative delirium struggled to compensate for its decreased function although they had more decreased gray matter volume than those without one. Partial correlation also showed a negative correlation between K-DRS and the connectivity strengths in the inferior frontal gyrus and caudate. It is supposed that enhanced connectivity association between the inferior frontal cortex and caudate nucleus may help to prevent exacerbation of delirious symptoms and facilitate earlier recovery from altered consciousness.

Second, regarding the involvement of bilateral insula in functionally greater association with the temporal gyrus or caudate nucleus, a report showed that the electrical stimulation between the left claustrum and anterior insula disrupted consciousness, suggesting that the anterior insula was an important part of a network that subserves consciousness.[59] The insular was also suggested to be involved in conscious perception of errors.[60] In our study, bilateral insula also seemed to participate in recovery of consciousness by cooperating together with the caudate nucleus.

Third, among temporal lobe sub regions, superior temporal gyrus and transverse temporal gyrus showed to be functionally associated with the thalamo-cortical connectivity, including the caudate nucleus and inferior frontal cortex, and the insula during delirious state. In partial correlation, there was a negative correlation of K-DRS with functional connectivity between the superior temporal gyrus and inferior frontal gyrus. These results may suggest that temporal areas also support to restore consciousness. In studies on temporal lobe seizures, loss of consciousness is a dramatic clinical manifestation and its underlying mechanism was found to be correlated with the degree of synchronization in thalamo-cortical system.[61,62] While temporal lobe seizure occurs with loss of consciousness due to abnormal excessive or synchronous neuronal activity between thalamo-cortical regions and temporal areas, greater increase in functional connectivity between temporal areas and other brain regions that support conscious information processing during delirious state was considered as trials to raise reduced functional level to recover consciousness. It was striking that temporal areas were involved in consciousness-related processing because it has been known to play a role mainly in auditory processing, including language, and social cognition.[63] However, our study showed MMSE scores were associated with the amount of cortical atrophy in the temporal lobe sub-regions, showing the involvement of temporal areas in postoperative delirium occurrence with cognitive impairment. Other studies also insisted that Alzheimer's disease is associated with impaired consciousness by a deficit of controlled processes that require conscious processing of information or by disconnection between memory and consciousness.[64,65] These impairments are associated with temporal areas. All things considered, temporal areas are important brain regions to improve altered consciousness with thalamo-cortical brain regions in spite of impaired cortical volume.

In terms of cognition and attention, previous study reported a positive partial correlation between the left caudate nucleus volume and MMSE scores.[66] The degree of right to left caudate volume asymmetry also predicted attention deficit hyperactivity disorder in children by showing that smaller volume of the left caudate than right one was correlated with inattentiveness scores. In thalamo-cortical circuit, the disruption of this circuit has been reported in patients with obsessive compulsive disorder.[67] Therefore, thalamo-cortical brain regions in patients with postoperative delirium may be involved in alteration of not only consciousness, but also cognition or attention.

Moving focus on the posterior cingulate cortex/precuneus, this region also showed decreased gray matter volume in patients with postoperative delirium than in patients without one. However, there was no brain region with increased or decreased connectivity with the posterior cingulate cortex/precuneus for both between-group and within-group comparisons. This result was quite different from previous study, which reported that bilateral precuneus and bilateral dorsolateral prefrontal cortex showed positive correlations with the posterior cingulate cortex in the during-episode group than comparison group.[23] It could be explained that participants recruited in our study were about 10 years older than previous study. That means our study included more patients with Alzheimer's disease, thus it could cause considerable difference in brain condition. Additionally, present study used the posterior cingulate gyrus with different coordinates in functional connectivity analysis, so it may result in different results. To confirm our obtained result, functional connectivity analyses using the same seed regions as other studies would be needed in the further studies.

There are some limitations in this study. First, the effects of medication were not considered. Most patients were medicated for their various pre-existing medical conditions and some medications are more likely than others to be associated with delirium. However, we should consider the range of medications to be too diverse to quantify, and the contribution of each to delirium has not yet been proven. Particularly about antipsychotics, a recent review reported that there was no general effect on the fMRI signal.[68] Second, although delirium subtype existed, data analysis was performed altogether, so the differences of functional connectivity from subtype were not included in this study. Third, we collected paired scans in only 13 patients with delirium, so this reduced sample size may result in limited conclusions.

V. CONCLUSION

The present study demonstrates distinctive neural correlates to predict postoperative delirium in patients with hip fracture using preoperative magnetic resonance imaging. Brain volume comparison suggests that patients with postoperative delirium have similar features with Alzheimer′s disease, particularly reduced concentration in the frontal areas, temporal areas, and caudate nucleus in accordance with cognitive impairment. Widespread impairment in the white matter tracts, including the superior and inferior longitudinal fasciculus, implies a disconnection between long-distance brain regions. Nevertheless, increased connectivity of the bilateral temporal brain regions with thalamo-cortical brain regions, including the caudate nucleus and inferior frontal gyrus, and insula on delirious state, supports compensatory response to prevent exacerbation of delirium symptoms and induce earlier restoration from altered consciousness.

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ABSTRACT (IN KOREAN)

전향적 자기공명영상 분석을 이용한 뇌에서 수술 후 섬망의 위험요인 규명

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신 정 은

섬망은 의식과 주의력 손상을 동반한 인지의 갑작스런 변화, 동요를 특징으로 하는 급성 혼돈 상태이다. 대부분 수일 내에 사라지지만 섬망이 주는 영향은 의학적 예후와 경제적 비용 면에서 막대하다. 현 연구는 수술 후 섬망 발생을 예측할 수 있는 뇌 내 표지자를 규명하는 것을 목표로 하였다. 수술 전 고관절 골절 환자의 인지 손상을 측정하고, 자기공명영상을 촬영하였다. 수술 후에는 7 일간 환자의 섬망 여부를 평가하였고, 섬망 발생에 따라 섬망 발생 당일이나 섬망 평가 마지막 날 재촬영을 시행하였다. 그리고 해부학적, 기능적 데이타는 화소 기반 형태분석, 확산 텐서 영상, 기능적 연결 분석으로 시행하였다. 수술 후 섬망군은 비섬망군에 비해 뇌 내 용량과 뇌실

용량의 증가가 나타났고, 내측 전두엽, 대상회/쐐기앞소엽, 상측두회, 횡측두회, 미상핵에서는 용량 감소가 나타났는데 이러한 결과는 알츠하이머 환자의 뇌 특징과 유사했다. 또한 위/아래 세로다발, 뇌량, 외포를 포함한 뇌 전반의 백질의 밀도가 감소된 걸 관찰할 수 있었다. 기능적 연결 분석에서는 섬망군이 미상핵, 뇌섬엽, 상측두회 내에서 비섬망군에 비해 기능적 연결이 나타났고, 섬망 관련 임상척도와의 편상관 분석에서 섬망증상 심각도와 섬망기간이 하전두회, 미상핵을 포함한 시상-피질 회로 영역과 상측두회 사이의 기능적 연결과의 부적 상관관계를 보였다. 이 연구는 측두엽과 미상핵을 포함한 피질 위축과 뇌 전반에 걸친 피질간 연결 손상이 수술 후 섬망 발생에 관여하고 있다고 생각된다. 해부학적 위축 및 손상에도 불구하고 섬망 중 이들 영역과 시상-피질 뇌 영역 간의 기능적 연결 증가는 섬망 지속을 막고 의식 회복을 촉진하기 위한 노력으로 풀이된다.

핵심되는 말: 수술 후 섬망, 화소 기반 형태분석, 확산 텐서 영상, 측두엽, 시상-피질 뇌 영역, 기능적 연결